

REMARKS

Claims 1 and 3 to 11 are currently pending and under examination in the application. No amendments are made by the present Reply. Reconsideration of the application is respectfully requested in view of the following remarks.

Rejections under 35 U.S.C. § 103

A. The Examiner rejected claims 1 and 3 to 5 under 35 U.S.C § 102(a) for alleged obviousness over Herman *et al.* (U.S. Patent No. 5,786,146, issued July 28, 1998) in view of Gerdes *et al.* (U.S. Patent 6,291,166, issued Sep. 18, 2001). The Examiner agreed at page 3 of the Action that Herman *et al.* do not disclose that a nucleic acid is bound to a solid phase and then the nucleic acid is deaminated. The Examiner asserted, however, that Gerdes *et al.* disclose a method of using solid phases to irreversibly capture RNA or DNA and teaches true, direct solid phase manipulation and analyses including enzyme recognition, hybridization and amplification. The Examiner then asserted that one of ordinary skill in the art would have been motivated to apply a solid phase bound DNA as taught by Gerdes *et al.* in the method of Herman *et al.* because, as taught by Gerdes *et al.*, a solid phase bound nucleic acid can be directly and conveniently manipulated and can be applied in various ways, for example treating/manipulating/analyzing/amplifying nucleic acids. The Examiner further asserted that such a combination would have been *prima facie* obvious at the time of filing.

Applicants traverse this rejection and submit that the instant claims satisfy the requirement of non-obviousness over the cited references. In particular, neither Herman *et al.* nor Gerdes *et al.*, alone or in combination, teach or suggest each feature of the instant claims.

Specifically, as acknowledged by the Examiner at page 3 of the Action, Herman *et al.* fail to teach or even remotely suggest the active, recited step of performing a deamination reaction on solid phase, such as by “incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated”. To the contrary, Herman *et al.*, at best, perform deamination reactions in solution. In fact, it is not all surprising that Herman *et al.* fail to teach or suggest the recited step of performing a deamination reaction on solid phase, because a person skilled in the art at the time of filing would have expected such a reaction to

produce no useful results whatsoever. Indeed, at the time of filing, bisulfite ions were believed to interact only with cytosines that do not participate in base-pairing (*see* Items 5 and 12 of the Declaration of Dr. Markert-Hahn, submitted with the Amendment/Response filed April 15, 2008). In fact, single-stranded DNA was believed to interact with a solid phase as if it were participating in base-pairing (*see Id.*). Thus, bisulfite ions were not expected to be able to physically interact with the cytosines in single-stranded DNA bound to a solid phase (*see Id.*). Since bisulfite ions must physically interact with the cytosines in DNA to achieve deamination, a person skilled in the art at the time of filing would have expected a bisulfite reaction performed on solid phase, as recited in claim 1(b), to produce no useful results whatsoever. Accordingly, Herman *et al.*, or any other reference from the time of filing, would have no reason to recite the active, recited step of the present claims of incubating the solid phase bound nucleic acid in the presence of sulfite ions, whereby the nucleic acid is deaminated.

Gerdes *et al.* do not remedy the defects in Herman *et al.* Gerdes *et al.* is entirely silent on the use of the solid phase techniques described therein for use in bisulfite modification reactions. Gerdes *et al.*, at best, mention the use of solid phase matrices in purification methods to irreversibly capture RNA or DNA, and solid phase manipulation and analyses including enzyme recognition, hybridization and amplification, but this latter generic teaching is far more limited than appreciated by the Examiner. In particular, Gerdes *et al.* relates to a method of irreversibly binding and thus, permanently archiving, nucleic acid from specimens, thus allowing re-analysis of the same nucleic acid specimen an unlimited number of times, which is especially useful when the specimen is available in limited quantity or cannot be replaced (*see, e.g.*, column 2, lines 43-45 and column 4, lines 22-26 of Gerdes *et al.*). However, the utility of the invention described in Gerdes *et al.* requires that the nucleic acid is neither altered nor exhausted during analysis (*see, e.g.*, column 2, lines 45-47 of Gerdes *et al.*). This utility, however, in no way relates to chemically modifying nucleic acid molecules as recited in the instant claims. Indeed, what is suggested in Gerdes *et al.* as “direct solid phase manipulation” (*see, e.g.*, column 3, lines 39-49 of Gerdes *et al.*) is in fact limited to a manipulation of the solid phase bound nucleic acid by enzyme, hybridization, and/or amplification reactions (*see, e.g.*, column 4, lines 45-48 of Gerdes *et al.*). None of the exemplary uses described in Gerdes *et al.* relate to modifying nucleic

acid molecules as presently claimed, *i.e.*, carrying out a bisulfite reaction on solid-phase bound nucleic acid whereby the nucleic acid is deaminated. There is no teaching in Gerdes *et al.* that the solid phase bound nucleic acid might be chemically modified, let alone be subjected to bisulfite treatment. Gerdes *et al.*, therefore, fail to teach or suggest the use of solid phase immobilization, as described therein, with a nucleic acid modification reaction, such as with the bisulfite reaction recited in the instant claims.

Contrary to the expectations at the time of filing, the instant application demonstrates successful bisulfite reactions performed on solid phase bound nucleic acid (*see* Example 5). Applicant submits that Herman *et al.* and Gerdes *et al.*, alone or in combination, fail to teach or in any way suggest the active, recited step of performing a deamination reaction on solid phase, such as by incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated. Moreover, in view of the understanding in the art at the time of filing, as evidenced by the Declaration of Dr. Markert-Hahn and discussed above, a person skilled in the art at that time would have had no motivation to perform such a step with any expectation of success, let alone the requisite reasonable expectation of success. Both Herman *et al.* and Gerdes *et al.* fail to motivate a person of ordinary skill in the art to conduct the bisulfite reaction of Herman *et al.* on solid phase bound nucleic acid molecules with any reasonable expectation of success.

Indeed, the Examiner has failed to establish that the skilled artisan would have the requisite motivation to produce the claimed method and any reasonable expectation of success in doing so. Notwithstanding the absence of this required reasoning, Gerdes *et al.* clearly fail to provide any such motivation. In fact, the method of Gerdes *et al.* requires that the solid-phase bound nucleic acid is un-denatured, so as to allow analyses of the bound nucleic acids by interaction with other molecules. This, however, is in sharp contrast to Herman *et al.*, which requires denatured nucleic acids, making the teachings of these two references technically incompatible in the mind of a person skilled in the art at the time of the instant invention. Thus, Gerdes *et al.* basically relate to a different technical field than Herman *et al.* and the instant invention.

Since the requisite elements of a *prima facie* case of obviousness are missing, Herman *et al.* and Gerdes *et al.*, alone or in combination, fail to establish a *prima facie* case of obviousness over the presently claimed subject matter.

Given the deficiencies in both Herman *et al.* and Gerdes *et al.*, it is submitted that these references, alone or in combination, fail to render the instant claims obvious. The instant claims satisfy the requirements of non-obviousness, and respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

B. The Examiner rejected claims 6 to 11 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* in view of Gerdes *et al.* (as applied to claims 1 and 3 to 5 in section A above), and further in view of Weindel *et al.* (WO 01/37291, issued May 21, 2001). The Examiner agreed that Herman *et al.* do not disclose that the solid phase comprises a magnetic glass particle, a magnetic glass particle having a diameter between 0.5µm and 5µm, or the magnetic glass particle manufactured by the sol-gel method. However, the Examiner asserted that Weindel *et al.* disclose a magnetic glass particle, which can be used in nucleic acid purification. Further, the Examiner asserted that Weindel *et al.* disclose that the magnetic glass particle is a solid dispersion of small magnetic core in glass, the diameter of the particle is between 5 and 500nm, and the magnetic glass particle is used in nucleic acid purification from a sample containing cells. Still further, the Examiner asserted that Weindel *et al.* disclose that the advantage of this is its potential simplicity and high sensitivity. The Examiner then asserted that one of ordinary skill in the art would have been motivated to apply the magnetic glass particle of Weindel *et al.* in the method of Herman *et al.* as a solid support for converting cytosine bases to uracil bases in a nucleic acid because of the advantage of using the magnetic glass particle. The Examiner further asserted that such a combination would have been *prima facie* obvious at the time of filing.

Applicants traverse this rejection and submit that the instant claims satisfy the requirement of non-obviousness over the cited references. In particular, Herman *et al.*, Gerdes *et al.*, nor Weindel *et al.*, alone or in combination, teach or suggest each feature of the instant claims.

As detailed in section A above, Herman *et al.* fail to teach or in any way suggest the active recited step of incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated, as recited in independent claim 1, from which the instant claims depend. As discussed above, Gerdes *et al.* do not remedy this deficiency. Weindel *et al.* also do not remedy this deficiency, as this reference is similarly silent with respect to performing deamination reactions on solid phase bound nucleic acid, let alone on magnetic glass particle bound nucleic acids, as recited in claims 6 to 11. In fact, Weindel *et al.* are limited to teaching the use of the magnetic glass particles described therein for either nucleic acid purification protocols or standardized nucleic acid amplification reactions. In failing to teach or suggest each feature of the instant claims, the cited references in combination fail to establish the minimum requirements of a *prima facie* case of obviousness.

Moreover, even if a person skilled in the art at the time of filing combined the methods of Herman *et al.* Gerdes *et al.*, and Weindel *et al.*, as proposed by the Examiner at page 4, last paragraph, of the Action, such a person would not arrive at the presently claimed subject matter. To the contrary, the combination proposed by the Examiner does not teach a person skilled in the art to perform the deamination reactions on solid phase, as recited in independent claim 1, but instead teaches that person to perform such reactions in solution. Thus, a person skilled in the art at the time of filing would have had to embark on a whole new line of experimentation to arrive at the presently claimed method, which would have required that person to go against the expectations in the art at the time of filing, as discussed in section A above (*see, e.g.*, Items 5 and 12 of the Declaration of Dr. Markert-Hahn).

Given the deficiencies in Herman *et al.*, Gerdes *et al.*, and Weindel *et al.*, these references, alone or in combination, fail to render the instant claims obvious. Consequently, the instant claims satisfy the requirements of non-obviousness, and withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

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Applicants respectfully submit that all of the claims remaining in the application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,  
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